Intravenous Lidocaine for the Prevention of Cough: Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract: BACKGROUND It remains unclear to what extent intravenous lidocaine prevents cough and whether there is dose-responsiveness and risk of harm. METHODS We searched electronic databases to January 1, 2017 for randomized trials comparing intravenous lidocaine with placebo for the prevention of cough in surgical patients. Primary outcome was the incidence of cough. Data were analyzed using a random-effects model and were expressed as risk ratio (RR) and number needed to treat (NNT) with 95% confidence interval. RESULTS In 20 trials in adults (n = 3062) and 5 trials in children (n = 445), intravenous lidocaine 0.5-2 mg · kg was tested for the prevention of intubation-, extubation-, or opioid-induced cough. Twenty-two trials included only American Society of Anesthesiologists I or II patients; 3 trials (n = 99) also included American Society of Anesthesiologists III patients. Lidocaine was associated with a lower incidence of cough compared to placebo in adults and children, irrespective of dosage and cough etiology. Data from adults suggested dose-responsiveness; with 0.5 mg · kg, RR was 0.66 (0.50-0.88) and NNT was 8 (5.4-14.3); with 1 mg · kg, RR was 0.58 (0.49-0.69) and NNT was 7 (4.6-8.9); with 1.5 mg · kg, RR was 0.44 (0.33-0.58) and NNT was 5 (3.3-5.2); and with 2 mg · kg, RR was 0.39 (0.24-0.62) and NNT was 3 (2.0-3.4). Adverse effect reporting was sparse. CONCLUSIONS Within a range of 0.5-2 mg · kg, intravenous lidocaine dose dependently prevents intubation-, extubation-, and opioid-induced cough in adults and children with NNTs ranging from 8 to 3. The risk of harm in high-risk patients remains unknown.

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Intravenous Lidocaine for the Prevention of Cough: Systematic Review and Meta-analysis of Randomized Controlled Trials

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BACKGROUND: It remains unclear to what extent intravenous lidocaine prevents cough and whether there is dose-responsiveness and risk of harm.

METHODS: We searched electronic databases to January 1, 2017 for randomized trials comparing intravenous lidocaine with placebo for the prevention of cough in surgical patients. Primary outcome was the incidence of cough. Data were analyzed using a random-effects model and were expressed as risk ratio (RR) and number needed to treat (NNT) with 95% confidence interval.

RESULTS: In 20 trials in adults (n = 3062) and 5 trials in children (n = 445), intravenous lidocaine 0.5–2 mg·kg^{-1} was tested for the prevention of intubation-, extubation-, or opioid-induced cough. Twenty-two trials included only American Society of Anesthesiologists I or II patients; 3 trials (n = 99) also included American Society of Anesthesiologists III patients. Lidocaine was associated with a lower incidence of cough compared to placebo in adults and children, irrespective of dosage and cough etiology. Data from adults suggested dose-responsiveness; with 0.5 mg·kg^{-1}, RR was 0.66 (0.50–0.88) and NNT was 8 (5.4–14.3); with 1 mg·kg^{-1}, RR was 0.58 (0.49–0.69) and NNT was 7 (4.6–8.9); with 1.5 mg·kg^{-1}, RR was 0.44 (0.33–0.58) and NNT was 5 (3.3–5.2); and with 2 mg·kg^{-1}, RR was 0.39 (0.24–0.62) and NNT was 3 (2.0–3.4). Adverse effect reporting was sparse.

CONCLUSIONS: Within a range of 0.5–2 mg·kg^{-1}, intravenous lidocaine dose dependently prevents intubation-, extubation-, and opioid-induced cough in adults and children with NNTs ranging from 8 to 3. The risk of harm in high-risk patients remains unknown. (Anesth Analg XXX;XXX:00–00)

KEY POINTS

- **Question:** Does intravenous lidocaine prevent cough? Is there a dose-responsiveness and any risk of harm?
- **Findings:** Twenty-five trials and 3507 patients were included. Within a range of 0.5–2 mg·kg^{-1}, intravenous lidocaine dose dependently prevents intubation-, extubation-, and opioid-induced cough in adults and children. Adverse effect reporting was sparse. The risk of harm in high-risk patients remains unknown.
- **Meaning:** Intravenous lidocaine dose dependently prevents perioperative cough in adults and children. Further research on high-risk patients is warranted.

Cough during the perioperative period is usually transient and self-limiting. On emergence from anesthesia, cough may protect against aspiration. However, cough can also result in perioperative morbidity, including tachyarrhythmia, arterial hypertension, cardiovascular collapse, and airway complications,[1–9] and it may increase intracranial, intraabdominal, and intraocular pressure.[10] An effective technique for preventing cough would be desirable in many situations where patients are at a particular risk. Cough-preventing strategies have been proposed, such as "deep extubation,"[11,12] gargling with various substances,[13] or topical or intracuff lidocaine.[14]

The clinical relevance of intravenous (IV) lidocaine as a way to blunt cough during tracheal intubation is deserved by specific and challenging clinical circumstances where avoidance of neuromuscular blocking agents is recommended or even mandatory. These conditions could include, for instance, awake intubation for expected difficult airway management, airway obstruction in children, known severe allergy to neuromuscular blocking agents, or certain neuromuscular disorders (eg, myasthenia gravis).[15,16]

The efficacy of a single IV bolus of lidocaine for the prevention of cough in the perioperative period has been the subject of numerous randomized controlled trials (RCTs). Two systematic reviews have described the efficacy of IV lidocaine for the prevention of fentanyl-induced cough.[17,18]

It remains unclear though whether IV lidocaine is equally effective for the prevention of mechanically induced cough (eg, during tracheal intubation) as for the prevention of

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opioid-induced cough, whether it is effective in both adults and children, whether there is dose responsiveness, and what the adverse effect profile is. We set out to address these issues with a systematic review and meta-analysis of RCTs.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for the reporting of meta-analyses of RCTs.[19] A complete PRISMA 2009 checklist is provided in Supplemental Digital Content, Table 1, http://links.lww.com/AA/C531. A protocol of this systematic review has not been published but is available from the authors.

Search Strategy

Searches in PubMed, Embase, and Cochrane Central Register of Controlled Trials were performed independently by 2 authors (S.C., A.P.) to January 1, 2017 (PubMed search strategy; Supplemental Digital Content, Methods 1, http://links.lww.com/AA/C531). We selected RCTs comparing IV lidocaine with placebo or no treatment for the prevention of mechanically or pharmacologically induced cough in adults or children in the perioperative setting. We also searched reference lists of retrieved articles. We applied no language restriction. Authors of original studies were contacted when reported data were unclear. Data from conference proceedings and abstracts were not considered if they were not published as full articles.

Data Extraction and Quality Assessment

One author (S.C.) extracted relevant information from each selected study. These data were checked by a second author (A.P.). Disagreement was resolved by consensus with the third author (M.R.T.). We specifically extracted information on lidocaine regimens, time point of administration, and etiology of the cough (eg, at emergence of general anesthesia). We extracted dichotomous data on the incidence of cough with and without lidocaine. When relevant efficacy data were displayed in graphical format only, and the authors of the original studies did not respond to our queries, we were using Plot Digitizer (http://plotdigitizer.sourceforge.net), a freely accessible Java program, to digitize scanned plots and extract dichotomous data. We also extracted any information on potential lidocaine-related adverse events.

Two investigators (S.C., A.P.) independently evaluated the quality of data reporting of the included studies using a modified Oxford score.[20] That score considers the reporting and adequacy of randomization, allocation concealment, blinding, and description of dropouts, and it ranges from 1 to 7 points for an RCT, with higher scores indicating better quality. We regarded a score of 6–7 as high quality, 4–5 as moderate quality, and 1–3 as low quality. Discrepancies and disagreement were solved by consensus with the third author (M.R.T.).

Statistical Analysis

The primary outcome was the incidence of cough in adults or children. Individual trial and summary results were reported as relative risk (RR) with 95% confidence interval (CI). A P value ≤.05 was considered statistically significant. An inverse variance random-effects model was used. Statistical heterogeneity was assessed using Higgins I^2 test and Cochran Q test. Data from each trial were considered as per the intention-to-treat principle. We also computed numbers needed to treat (NNT) with 95% CI. Pooling data from all trials seemed inappropriate due to different populations (adults or children), cough etiologies, and lidocaine regimens. We, therefore, performed analyses stratified by cough etiologies (eg, at intubation, at extubation, and after opioid administration) and lidocaine regimens. Data from adults and children were examined separately. $\chi 2$ test was used to test for group differences (between cough etiologies and lidocaine regimens), with a P value ≤.05 considered statistically significant. In adults, we performed meta-regression analyses to evaluate the effect of lidocaine dose on the incidence of cough. We assessed publication bias in the adult population using 4 methods: funnel plot, Begg and Mazumdar test,[21] Egger test,[22] and trim-and-fill analysis. Meta-analyses were performed using Review Manager (RevMan [Computer program], Version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014).

RESULTS

Characteristics of Included Studies

A total of 1603 citations were examined. After exclusions of 1083 nonpertinent studies, 51 studies were retrieved as complete articles. Of these articles, 26 were excluded because they did not meet inclusion criteria (Figure 1 and Supplemental Digital Content, Results 1, http://links.lww.com/AA/C531). Finally, 25 RCTs (3507 patients) were

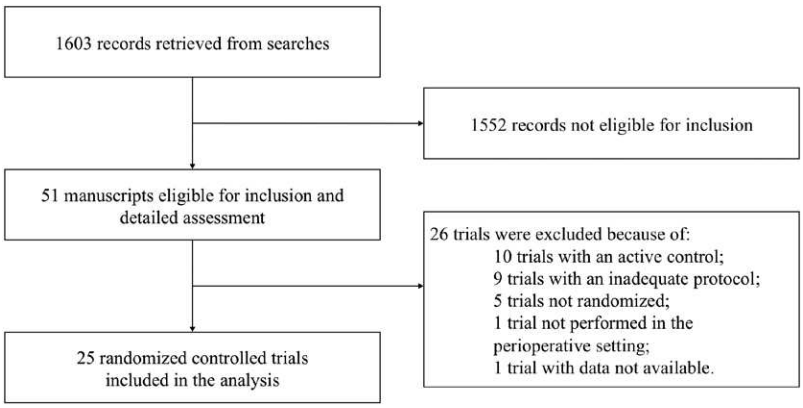

Figure 1. Flow diagram of retrieved, excluded, and eventually analyzed studies.

included (Table and Supplemental Digital Content, Table 2, http://links.lww.com/AA/C531).[23–48] In 10 trials, lidocaine was tested for the prevention of cough at extubation,[28,29,31,33,37,38,41,42,44,48] in 7 for the prevention of cough at intubation,[23,25,26,43,45–47] and in 8 for the prevention of cough after opioid administration.[24,27,30,34–36,39,40]

Twenty trials were performed in adults (3062 patients) and 5 in children (445 patients).[23,26,27,42,45] In 22 trials, patients were classified as American Society of Anesthesiologists (ASA) I or II; 3 trials (99 patients) included also ASA III patients.[29,33,38] All trials compared lidocaine with placebo, except 1 that had a no treatment control group.[29] Twenty-three trials administered saline 0.9% as a placebo; 2 studies[28,40] did not specify the nature of the placebo.

Lidocaine regimens were 0.5 mg·kg^{-1} IV in 6 trials,[24,27,34,40,46,47] 1 mg·kg^{-1} IV in 13,[25,27,28,30,31,33,35,37,40,41,44,46,47] 1.5 mg·kg^{-1} IV in 10,[29,31,39,40,42–44,46–48] and 2 mg·kg^{-1} IV in 7.[23,26,36,38,45–47] In 6 trials,[27,31,40,44,46,47] >1 lidocaine regimen was tested against placebo. In 1 trial,[25] outcome data had to be extracted using the Plot Digitizer.

The trials were published between 1985 and 2013. The number of patients per trial ranged from 19 to 502 (median, 80). Five trials came from India, 4 from Japan, 3 each from the United States and South Korea, 2 from Iran, and 1 each from the United Kingdom, Lebanon, Kosovo, Mexico, Spain, Taiwan, Turkey, and Israel. Twenty-three trials were published in English and 2 in Spanish.[34,44]

The median quality score of the studies was 5 (interquartile range, 5–6). Seven trials[28,30,31,39–41,48] were of high quality and 18 of moderate quality. None was of low quality (Supplemental Digital Content, Table 3, http://links.lww.com/AA/C531).

Efficacy With Different Cough Etiologies

The effect of lidocaine on cough at intubation, at extubation, and after opioid administration was assessed independently of the lidocaine regimen.

In 4 adult trials (551 patients) and 3 pediatric trials (185 patients), an IV lidocaine bolus was tested as a cough suppressant at induction of anesthesia. All patients were intubated without a neuromuscular blocking agent. Lidocaine reduced

Table. Characteristics of Included Trials

Trial	Population	Lidocaine Dosage, mg·kg^{-1}	Lidocaine Administration Time Point	Cough Stimulus	Cough Assessment Time Point	Type of Surgery	ASA Class	Sample Size
Aouad et al[23]	Pediatric	2	Before intubation	Intubation	Intubation	Adenotonsillectomy	I; II	90
Bang et al [24]	Adult	0.5	Before opioids	Opioids	Induction	Elective	I; II	158
Davidson and Gillespie[25]	Adult	1	Before intubation	Intubation	Intubation	Gynecological	I; II	60
Drenger and Pe'er[26]	Pediatric	2	Before intubation	Intubation	Intubation	Minor ocular	I; II	35
Gecaj-Gashi et al[27]	Pediatric	0.5; 1	Before opioids	Opioids	Induction	Elective	I; II	186
George et al[28]	Adult	1	Conclusion surgery	Extubation	Extubation	Elective craniotomy	I; II	76
Gonzalez et al[29]	Adult	1.5	Conclusion surgery	Extubation	Extubation	Elective general, orthopedic, urologic, plastic, vascular	I; II; III	50
Guler et al[30]	Adult	1	Before opioids	Opioids	Induction	Elective	I; II	200
Honarmand and Safavi[31]	Adult	1; 1.5	Before intubation	Extubation	Extubation	Abdominal, gynecological, and orthopedic	I; II	90
Khan et al[33]	Adult	1	Conclusion surgery	Extubation	Extubation	Gynecological and orthopedic	II; III	30
Kim et al[34]	Adult	0.5	Before opioids	Opioids	Induction	Elective	I; II	500
Lim et al[35]	Adult	1	Before opioids	Opioids	Induction	Elective	I; II	150
Lin et al[36]	Adult	2	Before opioids	Opioids	Induction	Elective	I; II	60
Mikawa et al[37]	Adult	1	Conclusion surgery	Extubation	Extubation	Minor gynecological and urological	I	50
Otero et al[38]	Adult	2	Conclusion surgery	Extubation	Extubation	Supratentorial neurosurgery	I; II; III	19
Pandey et al[39]	Adult	1.5	Before opioids	Opioids	Induction	Elective	I; II	502
Pandey et al[40]	Adult	0.5; 1; 1.5	Before opioids	Opioids	Induction	Elective	I; II	320
Saghaei et al[41]	Adult	1	Conclusion surgery	Extubation	Extubation	Cataract	I; II	186
Sanikop and Bhat[42]	Pediatric	1.5	Conclusion surgery	Extubation	Extubation	Cleft palate	I; II	74
Stoneham et al[43]	Adult	1.5	Before LM insertion	Intubation	Intubation	Elective day-hospital	I; II	75
Takekawa et al[44]	Adult	1; 1.5	Before intubation	Extubation	Extubation	Abdominal, gynecological, urological, and orthopedic	I; II	80
Warner et al[45]	Pediatric	2	Before intubation	Intubation	Intubation	Strabismus	I; II	60
Yukioka et al[46]	Adult	0.5; 1; 1.5; 2	Before intubation	Intubation	Intubation	General, gynecological, urological, and orthopedic	I	208
Yukioka et al[47]	Adult	0.5; 1; 1.5; 2	Before intubation	Intubation	Intubation	General, gynecological, urological, and orthopedic	I; II	208
Zamora Lozano et al[48]	Adult	1.5	Before intubation	Extubation	Extubation	Elective	I; II	40

Abbreviations: ASA, American Society of Anesthesiologists; LM, laryngeal mask.

the incidence of cough at intubation; for adults, RR was 0.48 (95% CI, 0.40–0.59), $P < .001$, P for heterogeneity = .62, $I^2 = 0\%$, and NNT was 4 (95% CI, 2.8–5.6) (Figure 2A); for children, RR was 0.44 (95% CI, 0.21–0.94), $P = .04$, P for heterogeneity = 0.36, $I^2 = 1\%$, and NNT was 7 (95% CI, 3.8–19.2) (Figure 2B).

Nine adult trials (621 patients) and 1 pediatric trial (74 patients) tested the efficacy of an IV lidocaine bolus on cough at extubation. In 7 of those trials, the lidocaine bolus was administered briefly before extubation, and in 3 trials, the lidocaine bolus was administered at induction, on average 121 minutes before extubation.[27,40,44] Lidocaine reduced the incidence of cough at extubation; for adults, RR was 0.61 (95% CI, 0.50–0.75), $P < .001$, P for heterogeneity = .22, $I^2 = 25\%$, and NNT was 5 (95% CI, 3.4–7.2) (Figure 2A); for children, RR was 0.44 (95% CI, 0.28–0.70), $P = .0005$, and NNT was 4 (95% CI, 2.2–11.8) (Figure 2B).

Seven adult trials (1890 patients) and 1 pediatric trial (186 patients) tested the efficacy of an IV lidocaine bolus on cough induced by the administration of an opioid (fentanyl[27,30,36,39,40] or remifentanil[24,34,35]). Lidocaine reduced the incidence of opioid-induced cough; for adults, RR was 0.48 (95% CI, 0.37–0.62), $P < .001$, P for heterogeneity = .11, $I^2 = 42\%$, and NNT was 7 (95% CI, 5.1–8.2) (Figure 2A); for children, RR was 0.29 (95% CI, 0.10–0.79), $P = .02$, and NNT was 5 (95% CI, 2.8–13.4) (Figure 2B).

Dose Responsiveness

We tested for dose responsiveness using data from adult trials only because the number of pediatric data was too limited. Combined data from all 3 settings were used (induction-, extubation-, and opioid-induced cough).

With lidocaine 0.5 mg·kg^{-1} (5 trials, 898 patients), RR was 0.66 (95% CI, 0.50–0.88) and NNT was 8 (95% CI, 5.4–14.3). With 1 mg·kg^{-1} (12 trials, 1112 patients), RR was 0.58 (95% CI, 0.49–0.69) and NNT was 7 (95% CI, 4.6–8.9). With 1.5 mg·kg^{-1} (9 trials, 1027 patients), RR was 0.44 (95% CI, 0.33–0.58) and NNT was 5 (95% CI, 3.3–5.2). With 2 mg·kg^{-1} (4 trials, 375 patients), RR was 0.39 (95% CI, 0.24–0.62) and NNT was 3 (95% CI, 2.0–3.4) (Figure 3). Meta-regression revealed a significant correlation between the dose of lidocaine and the incidence of cough ($P = .014$) (Supplemental Digital Content, Results 2, http://links.lww.com/AA/C531). Moreover, meta-regression suggested dose responsiveness when lidocaine was used at intubation and after opioid administration but not at extubation (Supplemental Digital Content, Results 2, http://links.lww.com/AA/C531).

Publication Bias

We were checking for publication bias with data of adult trials only because the number of pediatric data was too limited. When pooling data from all adult trials, the funnel

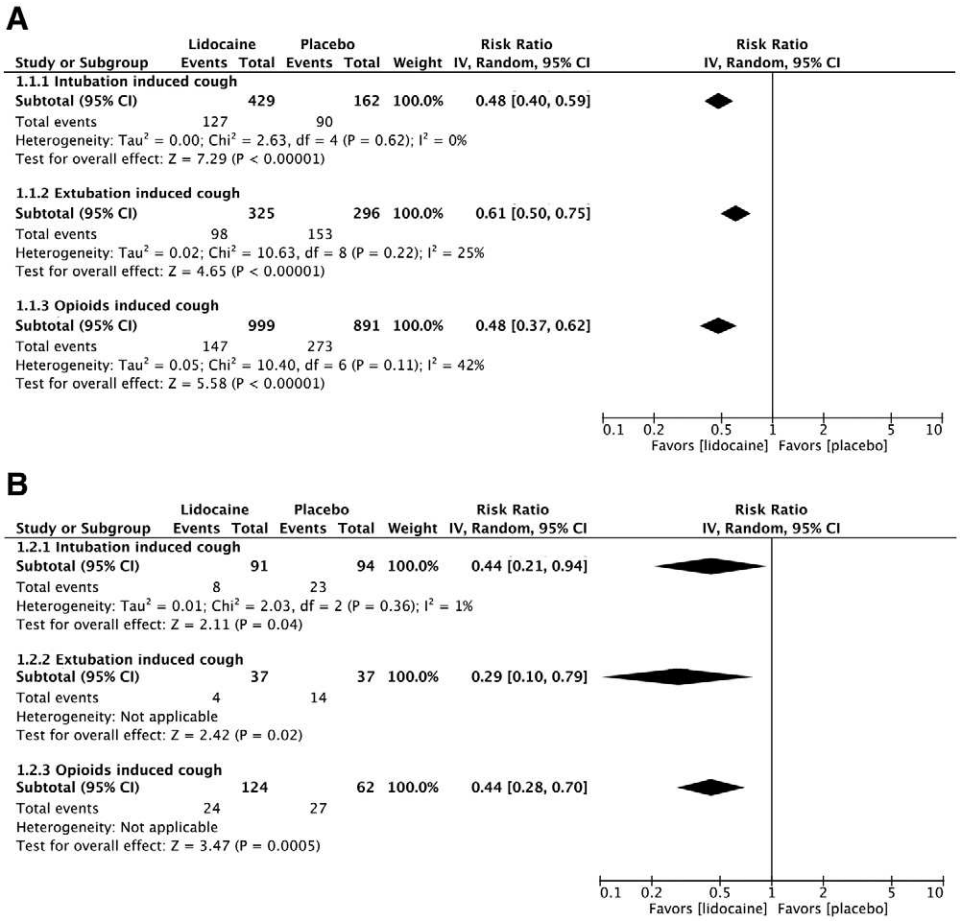

Figure 2. Impact of prophylactic intravenous lidocaine on cough incidence in different perioperative settings in adults (A) and children (B). Any lidocaine dose was included. Differences in group sizes are due to the inclusion of trials with multiple arms testing more than 1 lidocaine dose. CI indicates confidence interval; IV, inverse variance; Random, random-effects model.

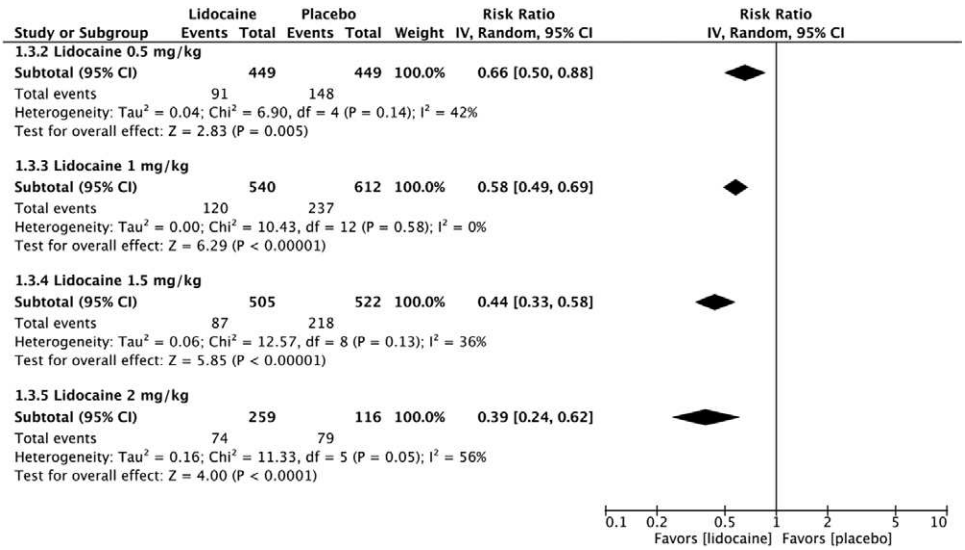

Figure 3. Impact of different prophylactic intravenous lidocaine doses on cough incidence in adults. Any lidocaine dose was included. Differences in group sizes are due to the inclusion of trials with multiple arms testing more than 1 lidocaine dose. CI indicates confidence interval; IV, inverse variance; Random, random-effects model.

plot showed asymmetry but with a minor effect on the effect estimate as indicated by the trim and fill. However, neither Begg and Mazumdar (P = .12) nor Egger regression asymmetry test (P = .10) confirmed the presence of significant publication bias (Supplemental Digital Content, Results 3, http://links.lww.com/AA/C531).

Adverse Effects

In 1 study including ASA I and II patients[41] and in 1 that included also ASA III patients,[29] a delayed recovery of consciousness after anesthesia was reported in some adult patients who had received lidocaine. Both studies failed to systematically report adverse events. In 1 trial including ASA I and II patients, 1 adult patient had "tinnitus" after the injection of lidocaine.[25] Ten studies (1160 patients) reported on the absence of adverse effects with lidocaine.[28,30,31,34,36,37,39,45–47] Two of those also included ASA III patients.[33,38] The remaining studies did not report on the presence or absence of adverse effects.

DISCUSSION

The main finding of this meta-analysis is that IV lidocaine, in a dose-dependent manner between 0.5 and 2.0 mg·kg^{-1}, may help in preventing cough at intubation, at extubation, and before opioid administration.

Cough in the perioperative setting is more often a nuisance than a real medical problem. Although cough is a protective mechanism, there are circumstances where surgical patients are vulnerable and susceptible to coughing and bucking. For instance, cough may trigger an abrupt increase in intracavity, intraocular, or intracranial pressure; may lead to arterial and venous hypertension, tachycardia, arrhythmia, and cardiovascular collapse; and may induce bronchospasm, laryngospasm, and other airway complications, for instance, in asthmatic patients. Also, coughing is a well-known adverse effect of opioid administration. Pharmacologically induced cough may be severe enough to result in morbidity.[49,50] In these patients, efficacious prevention of cough may be warranted. However, before routine administration of lidocaine for the suppression of cough can be advocated, the benefit and potential for harm must be carefully weighed. The underlying mechanisms of cough suppression with lidocaine are not clearly understood. Among the mechanisms that have been proposed are suppression of the excitation of airway sensory C fibers,[51] selective depression of pain transmission in the spinal cord,[52] and reduction in tonic neural discharge of active peripheral nerve fibers.[53]

It also remains unclear whether the time point of lidocaine administration is important. In 3 studies, the lidocaine bolus was given before intubation, although the cough-suppressing effect was tested at extubation or postoperatively only.[31,44,48] All 3 trials showed a significant cough-suppressing effect with lidocaine. The half-time of IV lidocaine is approximately 2 hours.[54,55] This may explain why a cough-suppressing effect may last until the end of a short surgical procedure. It has also been suggested that the cough pathway is sensitized in a way similar to pain. Thus, the strong stimulation of laryngoscopy or of moving a tube intratracheally may excite sensory C fibers and produce secondary neuroplasticity accompanied by cough. Lidocaine may reduce released neuropeptides and secondary neural change.[44]

We were able to test for dose responsiveness comparing the efficacy of 4 IV regimens: 0.5, 1.0, 1.5, and 2.0 mg·kg^{-1}. To limit confounding and because the number of pediatric data was limited, we included data from adults only. Meta-regression suggested dose responsiveness. With the highest dose, 2 mg·kg^{-1}, 1 in 3 patients will not cough who would have done so had they not received lidocaine. With 0.5 mg·kg^{-1}, the NNT was 8.

This begs the question as to the toxicity of IV lidocaine and whether there is dose responsiveness for harm too. In 2 studies, some patients from the lidocaine group regained consciousness later than the control patients, although sedation was not searched for systematically.[24,37] Many studies did not report on the presence or absence of adverse effects. We do not know whether no adverse effects occurred or whether they did but were not reported. Also, trials that included some adult ASA III patients did not specify whether adverse effects happened primarily in high-risk patients. IV lidocaine is frequently used for the treatment of cardiac arrhythmia,[56] for systemic analgesia,[57] for the prevention of pain on

injection of propofol,[58] and for blunting deleterious hemodynamic effects during laryngoscopy and extubation.[45,59–61] Recommended IV regimens for these indications range from 1 to 2 mg·kg^{-1}, and within this range, no major adverse effects have been reported.[61–63] Even higher doses result in plasma concentrations of about 2 µg·mL^{-1} that are still below toxic levels.[64,65] For the treatment of chronic pain, IV regimens up to 5 mg·kg^{-1} have been recommended.[66,67]

Seven trials, 3 in adults and 4 in children, that tested the cough-suppressing efficacy of lidocaine at induction used an intubation technique without muscle relaxants. The routine use of such a technique is of questionable value given that intubation without muscle relaxants may increase morbidity of the upper airway.[68]

We performed various subgroup analyses to test for the robustness of the results. The only factor that was shown to have an impact on efficacy was the dose. We were unable to show a difference in efficacy between adults and children or among different cough-inducing settings.

This meta-analysis has some limitations, most of which are related to weaknesses of the original trials. First, and perhaps most important, all studies were monocentric, and most were of small size. Second, pooling together different trials with different settings or lidocaine dosages improves power and applicability of the analyses but may overestimate treatment effects in subpopulations. Third, adverse effect reporting was poor. Also, lidocaine has not been tested in high-risk populations, for instance, patients with arrhythmia or patients undergoing cardiac surgery or interventional cardiac procedures. Fourth, most trials reported only the incidence of cough; in this context, decreasing intensity may be as important as decreasing the incidence. Finally, we concentrated on prevention of cough. It may be of clinical relevance to know the efficacy of IV lidocaine for the treatment of established cough.

CONCLUSIONS

A single IV bolus of lidocaine may help prevent cough at intubation, at extubation, and after opioid administration in adults and children. In adults, there is evidence of dose responsiveness between 0.5 and 2.0 mg·kg^{-1}; the NNT for the prevention of cough with the most efficacious regimen tested, 2 mg·kg^{-1}, is 3. In low-risk patients (ASA I or II), within the tested dose range, no significant adverse events were reported. The risk of adverse effects and harm in high-risk patients remains unknown.

DISCLOSURES

Name: Sara Clivio, MD.
Contribution: This author helped conceive the study, write the protocol draft, perform the literature searches, extract the data, perform the statistical analysis, write the article draft, and approve the final version of the manuscript.
Conflicts of Interest: None.
Name: Alessandro Putzu, MD.
Contribution: This author helped conceive the study, write the protocol draft, perform the literature searches, extract the data, perform the statistical analysis, write the article draft, and approve the final version of the manuscript.
Conflicts of Interest: None.
Name: Martin R. Tramèr, MD, DPhil.
Contribution: This author helped participate in the study conception, analysis interpretation, and article writing; and approve the final version of the manuscript.
Conflicts of Interest: M. R. Tramèr is the Editor-in-Chief of the *European Journal of Anaesthesiology*.
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